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FOLEY & LARDNER LLP			MUMMERT, STEPHANIE KANE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

11

<b>Office Action Summary</b>	<b>Application No.</b> 10/714,508	<b>Applicant(s)</b> QU ET AL.	
	<b>Examiner</b> Stephanie K. Mummert, Ph.D.	<b>Art Unit</b> 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on 23 June 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 2 and 40-72 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2 and 40-72 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's amendment filed on June 23, 2006 is acknowledged and has been entered. Claims 2 has been amended. Claims 1 and 3-39 have been canceled. Claims 40-72 have been added. Claims 2 and 40-72 are pending.

Claims 2 and 40-72 are discussed in this Office action.

Applicant's arguments with respect to claim 2 have been considered but are moot in view of the new ground(s) of rejection necessitated by Applicant's amendment to the claims.

1. All of the remaining amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**This action is made FINAL as necessitated by Applicant's amendment to the claims.**

### ***PREVIOUS REJECTIONS***

The rejections of claims 1 and 3-39 are withdrawn in view of Applicant's cancellation of the claims.

***Claim Rejections - 35 USC § 103***

1. Claims 2, 40-48, 50 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

With regard to claim 2 and 67, Lindpainter teaches a method of determining an angiotensin converting enzyme genotype in a sample comprising:

- a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 707, 'determination of ACE genotype' heading, where a first primer pair was used to amplify the D or I alleles and a third and fourth insertion specific primer pair was used to re-amplify certain samples and where it is noted that the reaction yields a 335 bp amplicon only in the presence of an I allele and no product in samples heterozygous DD); and
- b) detecting a homozygous ACE genotype by the production of one or two amplification products and a heterozygous ACE genotype by the production of three amplification products (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597

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bp for I allele and 335 bp are all resolved, where it is noted that the reaction yields a 335 bp amplicon only in the presence of an I allele and no product in samples heterozygous DD).

With regard to claims 40 and 68, Linpainter teaches an embodiment of claims 2 and 67, wherein said amplification reaction is by polymerase chain reaction (p. 707, col. 2, 'determination of ACE genotypes' heading, where D and I alleles were identified on the basis of polymerase chain reaction amplification).

With regard to claims 41 and 69, Lindpainter teaches an embodiment of claims 2 and 67, wherein the sample is a human sample (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at -80oC).

With regard to claim 42, Lindpainter teaches an embodiment of claim 41, wherein the method distinguishes between genotypes selected from the group consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Figure 1, where II, ID and DD genotypes are disclosed).

With regard to claim 43, Lindpainter teaches an embodiment of claim 41, wherein the DNA is undegraded DNA (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at -80oC).

With regard to 44, Lindpainter teaches an embodiment of claim 43, wherein the sample is a tissue sample (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at -80oC).

With regard to claim 45 and 46, Lindpainter teaches an embodiment of claim 44, wherein the sample is selected from the group consisting of: blood (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at  $-80^{\circ}\text{C}$ ).

With regard to claim 47, Lindpainter teaches an embodiment of claim 41, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claim 48, Lindpainter teaches an embodiment of claim 41, wherein the ACE sequence is a 287 bp nonsense DNA domain (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claims 50 and 70, Lindpainter teaches an embodiment of claims 41 and 67, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at  $-80^{\circ}\text{C}$ ).

Regarding claim 2, Lindpainter does not teach that the amplification reaction is carried out with three separate primers in a single amplification reaction.

Lin teaches amplification using three primers simultaneously in a single amplification reaction.

With regard to claim 2, Lin teaches a method of determining an angiotensin converting enzyme (ACE) genotype in a sample comprising:

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amplifying DNA in a single amplification reaction from a sample (p. 662, col. 1, 'genotyping of ACE gene I/D allele by conventional PCR' and col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the genotyping analysis of the ACE genotype, with three primers included in a PCR reaction simultaneously taught by Lin into the method of ACE genotyping with Lindpainter with a reasonable expectation for success. Both Lindpainter and Lin teach methods focused on the amplification of the 287 bp Alu insertion region within exon 16 of the ACE gene and both teach the inclusion of an insertion specific primer. The multiplexed real-time PCR amplification technique taught by Lin "takes advantage of the SYBR Green I fluorescent dye for real-time detection of PCR product and, based on the length and nucleotide contents, for the melting curve analysis of PCR products" (p. 661, col. 2 to p. 662, col. 1). Furthermore, the technique taught by Lin "provides a rapid and sensitive way for detection of ACE gene I/D polymorphism in clinical specimens" and "the applicability of real-time PCR to a high-throughput 96-well format should further reduce the overall time spent per sample and should be suitable for large-scale screening or research" (p. 665, col. 2). One of ordinary skill in the art would have recognized the benefit provided by the real-time PCR application taught by Lin and would therefore have been motivated to apply the technique to the method taught by Lindpainter with a reasonable expectation for success.

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2. Claims 2, 40-48, 50 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teranishi et al. (Journal of Hypertension, 1999, vol. 17, p. 351-356) in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666). Teranishi discloses an investigation of the association between the insertion/deletion polymorphism in the angiotensin converting enzyme and the microvascular structure of patients with non-Diabetic renal disease (Abstract).

With regard to claim 2 and 67, Teranishi teaches a method of determining an angiotensin converting enzyme genotype in a sample comprising:

- a) amplifying DNA from the sample with a i) first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 352, col. 1 'determination of angiotensin converting enzyme genotype' heading, where a first pair of primers results in a 190 bp fragment for the deletion, and a 490 bp fragment for the insertion, and a third insertion-specific primer results in a 408 bp PCR product in the presence of at least one insertion allele); and
- b) detecting a homozygous ACE genotype by the production of one or two amplification products and a heterozygous ACE genotype by the production of three amplification products (p. 352, col. 1 'determination of angiotensin converting enzyme genotype' heading, where a first pair of primers results in a 190 bp fragment for the deletion, and a 490 bp fragment for the insertion, and a third insertion-specific primer results in a 408 bp PCR product in the presence of at least one insertion allele, yielding one or two products for a homozygous D or I alleles and three amplicons in the presence of a heterozygous sample).



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With regard to claims 40 and 68, Teranishi teaches an embodiment of claims 2 and 67, wherein said amplification is by polymerase chain reaction (p. 352, col. 2, 'determination of angiotensin converting enzyme genotype' heading, where the I/D, II and DD genotypes of the ACE gene were determined by PCR).

With regard to claims 41 and 69, Teranishi teaches an embodiment of claims 2 and 67, wherein the sample is a human sample (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 42, Teranishi teaches an embodiment of claim 3, wherein the method distinguishes between genotypes selected from the group consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Table 1, where II, ID and DD genotypes are disclosed in classifying patients).

With regard to claim 43, Teranishi teaches an embodiment of claim 3, wherein the DNA is undegraded DNA (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to 44, Teranishi teaches an embodiment of claim 5, wherein the sample is a tissue sample (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype'

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heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 45 and 46, Teranishi teaches an embodiment of claim 6, wherein the sample is selected from the group consisting of: blood (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

With regard to claim 47, Teranishi teaches an embodiment of claim 3, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 351, col. 1, where the details of the ACE gene sequence and the polymorphism are disclosed).

With regard to claim 48, Teranishi teaches an embodiment of claim 3, wherein the ACE sequence is a 287 bp nonsense DNA domain (p. 351, col. 1, where the details of the ACE gene sequence and the polymorphism are disclosed).

With regard to claims 50 and 70, Teranishi teaches an embodiment of claims 2 and 67, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (p. 352, col. 1, 'subjects' heading, where 56 patients with nondiabetic renal disease were studied and p. 352, col. 1, 'determination of angiotensin converting enzyme genotype' heading, where genomic DNA was isolated from peripheral leukocytes in a whole-blood sample).

Regarding claim 2, Teranishi does not teach that the amplification reaction is carried out with three separate primers in a single amplification reaction.

Lin teaches amplification using three primers simultaneously in a single amplification reaction.

With regard to claim 2, Lin teaches a method of determining an angiotensin converting enzyme (ACE) genotype in a sample comprising:  
amplifying DNA in a single amplification reaction from a sample (p. 662, col. 1, 'genotyping of ACE gene I/D allele by conventional PCR' and col. 2, 'genotyping of ACE gene I/D allele by real-time PCR and melting curve analysis' heading, where ACE1-3 primers are included in a single amplification reaction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the genotyping analysis of the ACE genotype, with three primers included in a PCR reaction simultaneously taught by Lin into the method of ACE genotyping with Teranishi with a reasonable expectation for success. Both Teranishi and Lin teach methods focused on the amplification of the 287 bp Alu insertion region within exon 16 of the ACE gene and both teach the inclusion of an insertion specific primer. The multiplexed real-time PCR amplification technique taught by Lin "takes advantage of the SYBR Green I fluorescent dye for real-time detection of PCR product and, based on the length and nucleotide contents, for the melting curve analysis of PCR products" (p. 661, col. 2 to p. 662, col. 1). Furthermore, the technique taught by Lin "provides a rapid and sensitive way for detection of ACE gene I/D polymorphism in clinical specimens" and "the applicability of real-time PCR to a high-throughput 96-well format should further reduce the overall time spent per sample and should be suitable for large-scale screening or research" (p. 665, col. 2). One of ordinary skill in the art would have recognized the benefit provided by the multiplexed real-time PCR application taught by Lin and would therefore have been motivated to apply the technique to the method taught by Teranishi with a reasonable expectation for success.

3. Claims 49 and 51-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666) as applies to claims 2, 40-48, 50 and 67-70 above and further in view of Soubrier et al. (US Patent 5,736,323; April 1998) and Buck et al. (Biotechniques (1999) 27(3):528-536). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter in view of Lin teaches all of the limitations of claims 2, 40-48, 50 and 67-70 as recited in the 103 rejection stated above.

With regard to claim 51 and 52, Lindpainter teaches an embodiment of claim 41 and 49, wherein the nucleic acid products consist of a first nucleic acid fragment of approximately 123 base pairs, a second nucleic acid fragment of approximately 157 base pairs, and a third nucleic acid fragment of approximately 410 base pairs (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved and where 319 is approximately 123 bp, 335 is approximately 157 bp and 597 is approximately 410 bp).

With regard to claim 53, Lindpainter teaches an embodiment of claim 52, wherein:  
a) when the first nucleic acid fragment is not present and the second and third nucleic acid fragments are present, the genotype is I/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype); and

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b) when the first nucleic acid fragment is present and the second and the third nucleic acid fragments are not present, the genotype is D/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype).

With regard to claim 55, Lindpainter teaches an embodiment of claim 54, wherein the amplification is by polymerase chain reaction (p. 707, col. 2, 'determination of ACE genotypes' heading, where D and I alleles were identified on the basis of polymerase chain reaction amplification).

With regard to claim 56, Lindpainter teaches an embodiment of claim 55, wherein the method distinguishes between genotypes, selected from the group consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Figure 1, where II, ID and DD genotypes are disclosed).

With regard to claim 57, Lindpainter teaches an embodiment of claim 55, wherein the ACE sequence resides on intron 16 of chromosome 17q23 (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claim 58, Lindpainter teaches an embodiment of claim 55, wherein the ACE sequence is a 287 base pair nonsense DNA domain (p. 706, col. 1, where the details of the ACE gene polymorphism are detailed).

With regard to claim 59, Lindpainter teaches an embodiment of claim 55, wherein the DNA sample is from a source selected from the group consisting of: a biological fluid (p. 706, col. 2, 'study population' heading, where 1250 patients with ischemic heart disease were

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identified from the Physicians Health Study, and where these samples were submitted in EDTA-anticoagulated blood samples for storage at  $-80^{\circ}\text{C}$ ).

With regard to claim 60, Lindpainter teaches an embodiment of claim 55, wherein the nucleic acid products consist of a first nucleic acid fragment of 123 base pairs, a second nucleic acid fragment of 157 base pairs and a third nucleic acid fragment of 410 base pairs (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved and where 319 is approximately 123 bp, 335 is approximately 157 bp and 597 is approximately 410 bp).

With regard to claim 61, Lindpainter teaches an embodiment of claim 60, wherein:

- a) when the first nucleic acid fragment is not present and the second and third nucleic acid fragments are present, the genotype is I/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype); and
- b) when the first nucleic acid fragment is present and the second and the third nucleic acid fragments are not present, the genotype is D/D (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and the third amplicon of 335 bp is present in the presence of an I allele and no product for a DD genotype).

Lindpainter does not teach the limitation of claims 49 and 54, c) wherein the first pair of flanking primers have the nucleic acid sequences SEQ ID NO: 1, SEQ ID NO:2 and the third primer has the nucleic acid sequence of SEQ ID NO:3.

Soubrier teaches the full-length sequence of intron 16 of the angiotensin converting enzyme and teaches the optimal location for primers for the amplification of the insertion region (Abstract, Figures 2A-B, col. 2, lines 9-50).

With regard to claim 49 and 54, Soubrier teaches an embodiment of claim 41 and 49, wherein the first pair of flanking primers have the nucleic acid sequence 5'-CCATCCTTTCTCCCATTTCTCT-3' (SEQ ID NO:1) and 5'-GGATGGTCTCGATCTCCTGA-3' (SEQ ID NO:2) and the third primer has the nucleic acid sequence 5'-CCTTAGCTCACCTCTGCTTGTA-3' (SEQ ID NO:3) (see attached search report, where there is an exact match between nt 1416-1437 of SEQ ID 3 of Soubrier, which matches the 22 nt of SEQ ID NO:1).

Regarding claims 51-52 and 60, while Lindpainter does not disclose the specific amplicon sizes recited within the claim, it would have been obvious to one of ordinary skill in the art that if the primer locations were changed the amplicon size would change accordingly. Thus, an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and sequence length could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to adjust and optimize the location of the primers taught by Lindpainter, including those disclosed within the instant application and disclosed generally by Soubrier.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of angiotensin converting enzyme sequences, and concerning which a biochemist of ordinary skill would have attempted to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and



that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states “The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Furthermore, beyond the equivalence of primers taught by Buck and the obviousness of varying the locations within a given sequence, both Lindpainter and Soubrier give specific guidance with regards to the location of specific primer sequences and these are in line with the location of the primers disclosed in the instant application. For example, Lindpainter notes that they “used an optimized primer pair to amplify the D and I alleles” (p. 707, col. 2, ‘determination of ace genotype’ heading). Soubrier teaches that “the invention relates more particularly to pairs of distinct fragments selected from those previously mentioned, which can be used to design primers which can be used in sequence amplification procedures” (col. 2, lines 26-31). Furthermore, Soubrier teaches that “as a result of using two primers located on either side of at least a part of the polymorphic region, it is possible to easily visualize the difference in size due to the presence of or absence of the insertion” (col. 4, lines 7-14). As Soubrier directly states a motivation to design primers within the sequence flanking the insertion in intron 16 of the ACE gene, it would have been obvious to combine the sequence disclosed by Soubrier with the additional step taught by Lindpainter of adding an additional primer(s) designed to hybridize directly within the insertion to arrive at the claimed invention with a reasonable expectation for success.

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4. Claims 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666) as applies to claims 2, 40-48, 50 and 67-70 above and further in view of van Bockxmeer et al. (Circulation, 1995, vol. 92, p. 2066-71). Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter teaches all of the limitations of claims 2, 40-48, 50 and 67-70 as recited in the 103 rejection stated above.

With regard to claim 62, Lindpainter teaches a method for identifying a patient with a heightened risk of suffering from a disease comprising:

- a) determining the angiotensin converting enzyme (ACE) genotype in a sample from the patient by amplifying DNA from the sample with a first pair of flanking primers that hybridize to nucleic acid sequences flanking an ACE gene sequence, the presence of which indicates the presence of a first ACE gene variant, and the absence of which indicates the presence of a second gene variant, and ii) a third primer that specifically binds to said ACE gene sequence and together with one of the flanking primers forms a second pair of primers (p. 707, 'determination of ACE genotype' heading, where a first primer pair was used to amplify the D or I alleles and a third and fourth insertion specific primer pair was used to re-amplify certain samples);
- b) detecting a homozygous ACE genotype by the production of one or two amplification products and a heterozygous ACE genotype by the production of three amplification products (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved).

With regard to claim 64, Lindpainter teaches an embodiment of claim 29, wherein the method distinguishes between genotypes selected from the group consisting of: insertion/insertion, insertion/deletion, deletion/deletion (Figure 1).

With regard to claim 65, Lindpainter teaches an embodiment of claim 29, wherein the genotype is determined by detecting the presence or absence of each of three nucleic acid products of the amplification reaction (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved).

Lindpainter does not teach the limitation of claim 62, recited as c) correlating the ACE genotype of the patient with a treatment regimen designed to treat or prevent one or more diseases selected from the group consisting of: myocardial infarction, ischemic and idiopathic dilated cardiomyopathy, sudden death in hypertrophic cardiomyopathy, coronary arteriosclerosis, and restenosis after percutaneous transluminal coronary angioplasty.

With regard to claim 62, van Bockxmeer teaches a method which correlates the ACE genotype of the patient with a treatment regimen designed to treat or prevent one or more diseases selected from the group consisting of: myocardial infarction and restenosis after percutaneous transluminal coronary angioplasty (Table 1, where ACE genotype was correlated between angioplasty patients and control subjects, Table 2, where patient groups are characterized in groups as either with or without restenosis, Table 3, where ACE genotypes were correlated with angioplasty patients with and without restenosis, Table 4, where ACE and ApoE genotypes were correlated with angioplasty patients with and without restenosis and Table 5, where changes in lesions were compared between patients with different ACE genotypes).

With regard to claim 63, van Bockxmeer teaches an embodiment of claim 29, wherein the treatment regimen is designed to treat myocardial infarction or coronary atherosclerosis (p. 3, 'subjects and protocol' heading, where the study was restricted to patients having elective percutaneous transluminal balloon coronary angioplasty (PTCA) of a previously untreated native coronary artery).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the genotyping technique taught by Lindpainter to the genotype association analysis taught by van Bockxmeer with a reasonable expectation for success. Both Lindpainter and van Bockxmeer are focused on studying the genotype of the angiotensin converting enzyme (ACE) and with the determination of any association between ACE genotype and treatment or risk of myocardial infarction. As noted by van Bockxmeer, "the ACE gene was postulated to be a candidate gene affecting the important clinical problem of restenosis after percutaneous transluminal balloon coronary angioplasty (PCTA) (Abstract). Given the obvious link between the studies conducted by Lindpainter and van Bockxmeer, it would have been obvious to substitute the genotyping method taught by Lindpainter to the method taught by van Bockxmeer with a reasonable expectation for success.

5. Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666) as applies to claims 2, 40-48, 50 and 67-70 above and further in view of van Bockxmeer et al. (Circulation, 1995, vol. 92, p. 2066-71) and further in view of Soubrier et al. (US Patent 5,736,323; April 1998) and Buck et al. (Biotechniques (1999) 27(3):528-536).

Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter teaches all of the limitations of claims 2, 40-48, 50 and 67-70 as recited in the 103 rejection stated above. Lindpainter does not teach the limitation of claim 66 wherein the first pair of flanking primers have the nucleic acid sequences SEQ ID NO: 1, SEQ ID NO:2 and the third primer has the nucleic acid sequence of SEQ ID NO:3.

Soubrier teaches the full-length sequence of intron 16 of the angiotensin converting enzyme and teaches the optimal location for primers for the amplification of the insertion region (Abstract, Figures 2A-B, col. 2, lines 9-50).

With regard to claim 66, Soubrier teaches an embodiment of claim 63, wherein the pair of flanking primers have the nucleic acid sequences 5'-CCATCCTTTCTCCCATTTCTCT-3' (SEQ ID NO:1) and 5'-GGATGGTCTCGATCTCCTGA-3' (SEQ ID NO:2) and the third primer has the nucleic acid sequence 5'-CCTTAGCTCACCTCTGCTTGTA-3' (SEQ ID NO:3) (see attached search report, where there is an exact match between nt 1416-1437 of SEQ ID 3 of Soubrier, which matches the 22 nt of SEQ ID NO:1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to adjust and optimize the location of the primers taught by Lindpainter, including those disclosed within the instant application and disclosed generally by Soubrier.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

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"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of angiotensin converting enzyme sequences, and concerning which a biochemist of ordinary skill would have attempted to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Furthermore, beyond the equivalence of primers taught by Buck and the obviousness of varying the locations within a given sequence, both Lindpainter and Soubrier give specific guidance with regards to the location of specific primer sequences and these are in line with the location of the primers disclosed in the instant application. For example, Lindpainter notes that they “used an optimized primer pair to amplify the D and I alleles” (p. 707, col. 2, ‘determination of ace genotype’ heading). Soubrier teaches that “the invention relates more particularly to pairs of distinct fragments selected from those previously mentioned, which can be used to design primers which can be used in sequence amplification procedures” (col. 2, lines 26-31). Furthermore, Soubrier teaches that “as a result of using two primers located on either side of at least a part of the polymorphic region, it is possible to easily visualize the difference in size due to the presence of or absence of the insertion” (col. 4, lines 7-14). As Soubrier directly states a motivation to design primers within the sequence flanking the insertion in intron 16 of the ACE gene, it would have been obvious to combine the sequence disclosed by Soubrier with the additional step taught by Lindpainter of adding an additional primer(s) designed to hybridize directly within the insertion to arrive at the claimed invention with a reasonable expectation for success.

6. Claims 71-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindpainter et al. (NEJM, 1995, vol. 332, no. 11, p. 706-711) in view of Lin et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-666) as applies to claims 2, 40-48, 50 and 67-70. Lindpainter teaches an evaluation of the association of angiotensin converting enzyme polymorphisms with the risk of ischemic heart disease (Abstract).

Lindpainter teaches all of the limitations of claims 2, 40-48, 50 and 67-70 as recited in the 103 rejection stated above.

With regard to claim 71 and 72, Lindpainter teaches an embodiment of claim 67, wherein the nucleic acid products consist of a first nucleic acid fragment of approximately 123 base pairs, a second nucleic acid fragment of approximately 157 base pairs, and a third nucleic acid fragment of approximately 410 base pairs (p. 707, 'determination of ACE genotype' heading, where amplicon sizes of 319 bp for D allele, 597 bp for I allele and 335 bp are all resolved and where 319 is approximately 123 bp, 335 is approximately 157 bp and 597 is approximately 410 bp).

Regarding claims 71-72, while Lindpainter does not disclose the specific amplicon sizes recited within the claim, it would have been obvious to one of ordinary skill in the art that if the primer locations were changed the amplicon size would change accordingly. Thus, an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and sequence length could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to adjust and optimize the location of the primers taught by Lindpainter, including those disclosed within the instant application and disclosed generally by Soubrier in



order to achieve the optimal resolution of the genotypes of the insertion and/or deletion alleles of the ACE gene, including amplicon sizes which meet the limitation of the method as claimed.

***Response to Arguments***

7. Applicant's arguments with respect to the rejection of claims 1-39 have been considered but are moot in view of the new ground(s) of rejection.

***Relevant Prior Art***

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Shanmugam et al. (PCR Methods and Applications, 1993, vol. 3, p. 120-121), Odawara et al. (Human Genetics, 1997, vol. 100, p. 163-166), Montgomery et al. (Circulation, 1997, vol. 96, p. 741-747), Frishberg et al. (Kidney International, 1998, vol. 54, p. 1843-2849), Pedersen-Bjergaard et al. (US PgPub 2003/0158090; August 2003) and Osterop et al. (Hypertension, 1998, vol. 32, p. 825-830) each disclose a variety of methods of amplification of the ACE insertion/deletion polymorphism within intron 16 using a third insertion-specific primer.

***Conclusion***

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

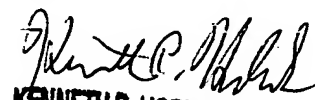
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Stephanie K Mummert, Ph.D.  
Examiner  
Art Unit 1637

  
KENNETH R. HORLICK, PH.D.  
PRIMARY EXAMINER

9/6/06